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THE INSPIRED SINEWAVE TECHNIQUE: A COMPARISON STUDY WITH BODY PLETHYSMOGRAPHY IN HEALTHY VOLUNTEERS

Phi Anh Phan, Cathy Zhang, Daniel Geer, Federico Formenti, Clive Hahn, and Andrew Farmery

Index Terms— **Lung Function Test, Functional Residual Capacity, Cardiac Output, Lung Inhomogeneity, Medical Device**

The inspired sinewave technique is a noninvasive method to measure airway dead space, functional residual capacity, pulmonary blood flow, and lung inhomogeneity simultaneously. The purpose of this study was to assess the repeatability and accuracy of the current device prototype in measuring functional residual capacity, and also participant comfort when using such the device. To assess within-session repeatability, six sinewave measurements were taken over 2-hour period in 17 healthy volunteers. To assess day-to-day repeatability, measurements were taken over 16 days in 3 volunteers. To assess accuracy, sinewave measurements were compared to body plethysmography in 44 healthy volunteers. Finally, 18 volunteers who experienced the inspired sinewave device, body plethysmography and spirometry were asked to rate the comfort of each technique on a scale of 1-10. The repeatability coefficients for dead space, functional residual capacity, and blood flow were 48.7 ml, 0.48L, and 2.4L/min respectively. Bland-Altman analyses showed a mean BIAS(SD) of -0.68(0.42)L for functional residual capacity when compared with body plethysmography. 14 out of 18 volunteers rated the inspired sinewave device as their preferred technique. The repeatability and accuracy of functional residual capacity measurements were found to be as good as other techniques in the literature. The high level of comfort and the non-requirement of patient effort meant that, if further refined, the inspired sinewave technique could be an attractive solution for difficult patient groups such as very young children, elderly, and ventilated patients.

I. Introduction

MEASUREMENT of key cardiorespiratory variables such as airways dead space (V_D), functional residual capacity (FRC), pulmonary blood flow (Q_P) and ventilation inhomogeneity has the potential to improve the care of ventilated and nonventilated patients [1]. In particular there has been a renewed interest in using these measurements to guide therapy in patients with acute lung injury [2]. However, most current techniques either require patient cooperation and/or rely heavily on the operator's expertise. Some systems used in ventilated patients require that users switch between breathing systems, interfering with the ventilatory mode, or require the use 100% oxygen.

For measuring cardiac output (CO) or pulmonary blood flow, of the notable techniques are thermodilution, Fick principle, oesophageal Doppler, and pulse contour analysis [3], [4]. , Each has its own limitations. Thermodilution via pulmonary artery catheters has been regarded the clinical standard for cardiac output monitoring for many years. However, its limitations are well known. These include invasiveness, associated complications, inaccuracy, and its clinical value when used to improve patient outcomes has been questioned [5]. The Fick principle using CO_2 rebreathing is another traditional method. It requires a propriety re-breathing circuit that is switched every few minutes to provide intermittent CO measurements. The presence of increased pulmonary shunt fraction and haemodynamic instability have been associated with decreased accuracy [6]. Oesophageal Doppler devices measure blood flow velocity in the descending aorta and estimate cardiac output by multiplying the velocity with the cross sectional area of the aorta. The required assumption of

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P. A. Phan is with the Nuffield Department of Clinical Neurosciences, Nuffield Division of Anaesthetics, University of Oxford, OX3 9DU. (e-mail: phi.phan@ndcn.ox.ac.uk)

C. Zhang is with GKT School of Medicine, King College of London, UK. (e-mail: cathy.zhang@kcl.ac.uk)

D. Geer is with the Queen's College, University of Oxford, UK. (e-mail: daniel.geer@queens.ox.ac.uk)

F. Formenti is with Centre of Human & Aerospace Physiological Sciences, King's College of London, UK (e-mail: federico.formenti@kcl.ac.uk)

C. E. W. Hahn is with the Nuffield Department of Clinical Neurosciences, Nuffield Division of Anaesthetics, University of Oxford, OX3 9DU. (e-mail: clive.hahn@nda.ox.ac.uk)

A. Farmery is with with the Nuffield Department of Clinical Neurosciences, Nuffield Division of Anaesthetics, University of Oxford, OX3 9DU. (e-mail: Andrew.farmery@nda.ox.ac.uk)

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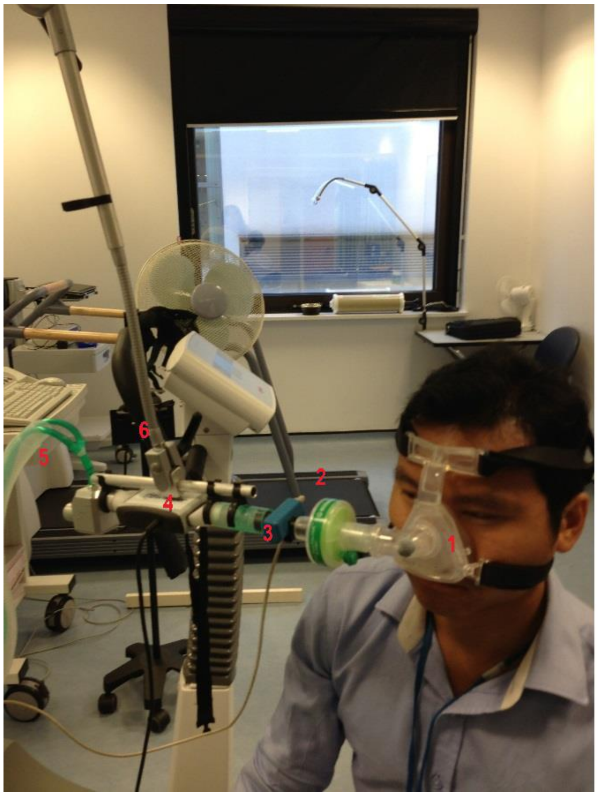

Fig. 1: The Inspired Sinewave Device. (1): nasal mask with seal; (2): bacterial and moisture filter; (3): N2O infrared sensor; (4): flow sensor; (5): gas mixing chamber; (6): articulated arm.

a fixed partition between flow to the cephalic vessels and to the ascending aorta may not be valid in patients with co-morbidities and during haemodynamic instability. Moreover, since ultrasound probe position is crucial to obtain accurate measurement, oesophageal Doppler devices are operator-dependent and studies have shown that 10-12 insertions are required to obtain accurate measurements [7]. Pulse pressure analysis is based on the principle that stroke volume can be continuously estimated by analyzing the arterial pressure waveform obtained from an arterial line [8]. The characteristics of the arterial pressure waveform is affected by individual vascular compliance, aortic impedance and peripheral arterial resistance. Pulse pressure analysis therefore may be of limited accuracy during periods of haemodynamic instability, i.e. rapid changes in vascular resistance. Overall, CO monitoring is still an active research field, with an ongoing debate on how these technologies are compared and validated.

For measuring FRC, body plethysmography, multi-breath nitrogen washout, helium dilution are the recommended techniques by the American Thoracic Society / European Respiratory Society Task Force [9]. Imaging techniques such as CT and MRI were also mentioned but not without raised controversies and critical questions around their uses. Measuring FRC on ventilated patients is not as readily available. Most existing lung function tests only treat the lung as a "balloon" and completely ignore the pulmonary blood recirculation, which is as important to the O2 uptake / CO2 removal process.

There is a need for a low cost bedside technique to measure lung function and pulmonary blood flow simultaneously, which is independent of patient effort, and therefore applicable to difficult patient groups such as children, the elderly, and ventilated patients. The inspired sinewave technique can potentially be such a technique.

The inspired sine-wave technique (IST) is a means of measuring these variable non-invasively without user input, interference with the breathing system or changing the mean inspired fractional oxygen. The underlying principle is that a sinusoidally modulated signal (in the form of the partial pressure of a tracer gas) is generated in the inspired air. This sinewave is damped in amplitude and shifted in phase by the lung and the pulmonary blood flow, and is distorted yet further by inhomogeneities in ventilation and perfusion. A mathematical model of the lung and body systems is used to process the flow and concentration data to recover the desired cardiopulmonary parameters.

The technique originated from the work of Zwart et al., where forced inspired sinusoids of halothane were used to determine average ventilation/perfusion ratios (V/Q) [10], [11]. Hahn et al. extended this idea to interrogate the cardiopulmonary system and began using patient safe-gases such as O_2 and low concentration of N_2O (3% mean) [12], [13]. They also extended the simple continuous lung model used by Zwart to more realistic tidal and multicompartmental models [14], [15]. Preliminary clinical studies with both animals [16] and healthy volunteers [17]–[19] showed promising results. Following recent developments on both hardware design and algorithms to improve accuracy/precision, the device has moved from the laboratory setting closer to the clinical environment [20].

This paper presents data comparing the IST's FRC measurements with that of body plethysmography. Assessment of the IST's blood flow measurement is not within the scope of this paper and will be the subject of a separate study. The aim is to assess the current repeatability and accuracy of the device prototype to measure FRC. We also aim to assess the comfort of using such a device in clinical settings.

II. Methods

A. The Inspired Sinewave Device

The Inspired SineWave Device (ISD; Fig. 1) operates by injecting small quantities of nitrous oxide (N2O) through a mixing chamber (5) into inspired air at a rate proportional to the instantaneous inspiratory rate using an ultrarapid feedback system. This allows the intra-breath concentration of tracer to be fixed, and forces the between-breath concentrations to follow a sinewave function around a set mean (~3%) and with a selectable frequency. An infrared mainstream N2O sensor (3) (SquareOne Technology) is

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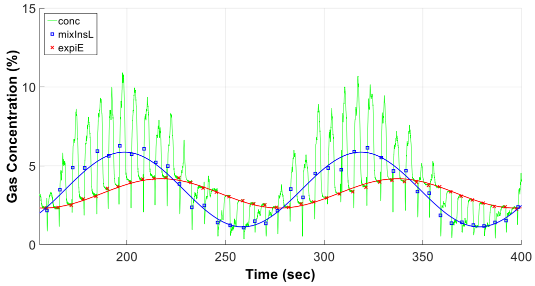

Fig. 2: An example of inspired and expired sinewaves of N_2O in an inspired sinewave technique test. The green line is N_2O concentration measured by the infrared mainstream sensor. The blue dots are the mean inspired concentration, whereas the red crosses are the end expired concentration. The blue and red sinewaves are the inspired and expired sinewaves respectively.

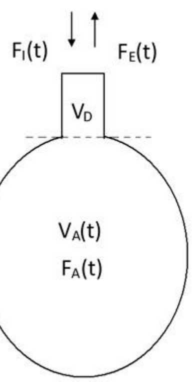

Fig. 3: One-compartment "balloon on a straw" lung model. $F_I(t)$ is the inspired concentration, $F_E(t)$ is the expired concentration, V_D is the airway deadspace, $V_A(t)$ is the lung/alveolar volume, and $F_A(t)$ is the alveolar concentration.

used to measure the N2O concentration in the inspired and expired air. An ultrasound flow meter (4) (VenThor – 22/2A) measures the airflow. A nasal mask (1) with a filter (2) is used to connect the system to a patient.

1) The inspired sinewave technique

The inspired sinewave technique to estimate lung volume and pulmonary blood flow has been detailed elsewhere [20]. The key steps are summarized here for convenience.

Fig 2 demonstrates a typical data set collected in an inspired sinewave test. To estimate the desired parameters, the lung is considered as a one-compartment "balloon on a straw" model (Fig 3). For 2 consecutive breaths (n-1) and n, the conservation of mass means that:

$$\begin{aligned}&\text{change of mass in lung} = \\ &\text{mass inhaled - mass exhaled - mass absorbed to the blood}\end{aligned} \tag{1}$$

The mass balance equation, therefore can be written as:

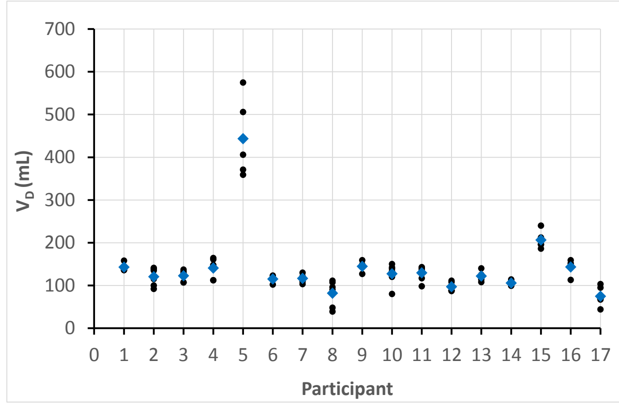

Fig. 4a

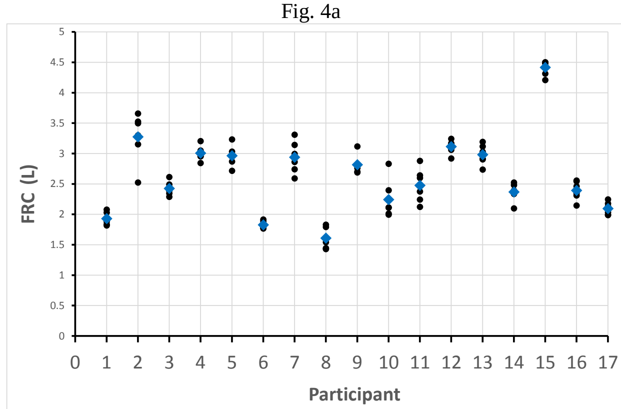

Fig. 4b

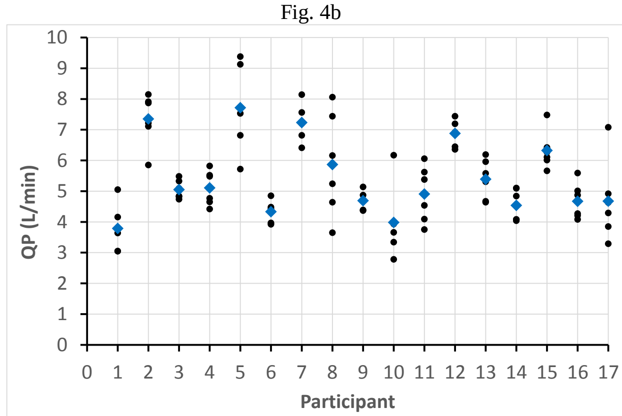

Fig. 4c

Fig. 4(a –c): repeated sinewave measurements of V_D, FRC, Q_P for 17 participants over 2 hours. Black dots are individual measurements. Blue diamonds are the average.

$$\begin{aligned}&V_A \times \left(F_{E,n} - F_{E,n-1}\right) + \lambda \times \dot{Q}_P \times \left(F_{E,n} - F_{\bar{v}}\right) \times \Delta t_n \\ &= V_D \times \left(F_{\bar{I},n} - F_{E,n-1}\right) + V_{T,n} \times \left(F_{E,n} - F_{\bar{I},n}\right)\end{aligned} \tag{2}$$

, in which:

V_A : the lung volume;

$\dot{Q}_P$: the pulmonary blood flow;

V_D : the deadspace, estimated from the Bohr method;

$F_{\bar{I},n}$: the mean inspired concentration of breath n^{th};

$F_{E,n-1}$, $F_{E,n}$: the end expired concentrations of breath (n-1) and n;

λ : the solubility of N_2O, 0.47;

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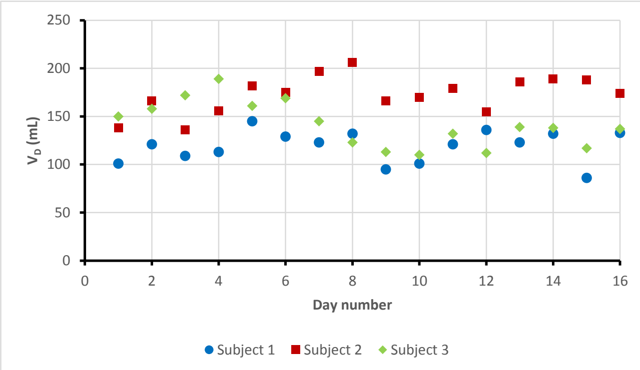

Fig. 5a

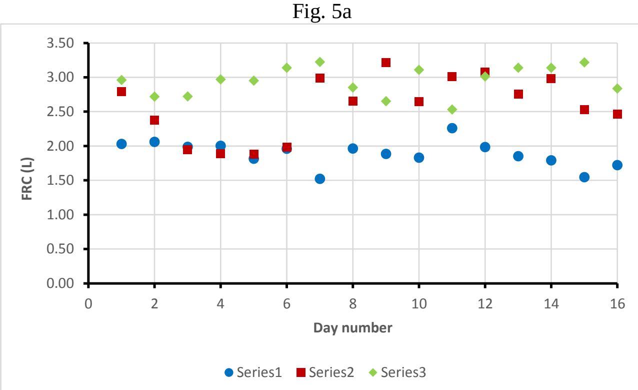

Fig. 5b

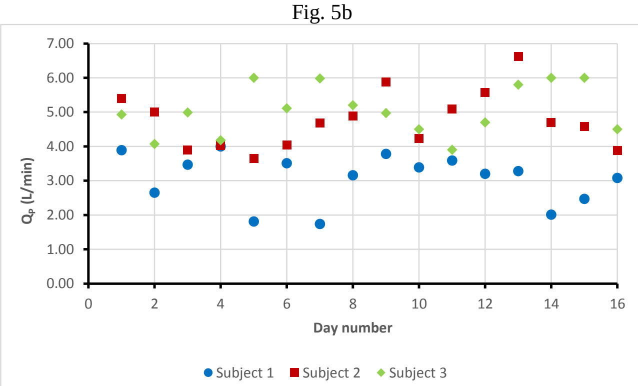

Fig. 5c

Fig.5(a-c): day-to-day repeated sinewave measurements for 3 participants over 16 days.

$F_{\bar{v}}$: the mixed venous concentration, assumed to equal to the mean of the inspired sinewave concentration at steady state;

Δt_n : the duration of breath nth;

$V_{T,n}$: the tidal volume of breath nth;

First, the deadspace V_D is estimated using the Bohr method applied to N2O signal:

$$V_D = V_T \frac{F_E - F_{\bar{E}}}{F_E - F_{\bar{I}}} \quad (3)$$

, in which $F_{\bar{E}}$ is the mean expired concentration. To compensate for the error associated with the non-uniform inspired concentration, a modified Bohr method has been proposed. The modified method improves the accuracy and repeatability of the airway deadspace estimation [21]. This improvement, in turn, leads to increased accuracy and repeatability in the estimation of the lung volume V_A and the pulmonary blood flow Q_P subsequently.

For a series of breaths, a set of linear equations can be established from eq (2) and solved for V_A and Q_P. FRC can then be calculated as sum of the V_D and V_A. Theoretically, three consecutive breaths would be sufficient to construct the linear equations to solve for V_A and Q_P. In practice, the use of all breaths within a complete sinewave period is recommended to improve repeatability. Interested readers can refer to [20] for more details.

For the purpose of this study, an inspired sinewave test consisted of 360sec of spontaneous breathing into the ISD with the sinewave period (T) set to be 180sec. More specifically, the first 100sec was used to bring the mixed venous concentration to the steady state, and the inspired sinewave was administered in the subsequent 260sec. The reported V_D, V_A, and Q_P were the mean values over the 260s of the sinewave.

B. *Experiment Setup*

The study was approved by the local research ethics committee at the medical sciences division, University of Oxford (Ref: MSD/IDREC/C1/2012/35) and written informed consent was obtained from all participants. All procedures conformed to the declaration of Helsinki.

1) Repeatability

Within-session repeatability. 17 healthy volunteers (10 male and 7 female, Mean (SD) age of 22(3.5)) were recruited for the study. Six tests were performed with each volunteer while they were sitting upright at rest over a two-hour period.

Day-to-day repeatability. In addition, 3 participants were tested once whilst resting supine, across 16 different days over a three-month period.

For both repeatability studies, mean V_D, FRC, Q_P were calculated, as well as standard deviations, coefficient of variations, repeatability coefficients, and repeatability r by ANOVA.

The coefficient of variation was defined as:

$$\text{Coefficient of Variation} = \frac{\text{Standard Deviation}}{\text{Mean}} \quad (4)$$

The reported coefficient of variation is the mean of individual coefficient of variations.

The repeatability coefficient was estimated as:

$$\text{Repeatability} = 1.96\sqrt{2}s_{\omega} \quad (5)$$

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Table 1: Within-session repeatability analysis. Participant 5 whose V_D measurements were consistently higher than normal 443(93.5)ml was excluded from the all statistical analysis.

	Individual mean range	Individual STD range	Overall Mean(STD)	Mean Coefficient of Variation	Repeatability coefficient	r (ANOVA)
V_D	74.7 – 443.4 ml	6.4 – 93.5 ml	123.8(33.9) ml	14.5%	48.7 ml	0.74
FRC	1.61 – 4.41 L	0.07 – 0.41 L	2.51(0.68) L	7.6%	0.48 L	0.90
Q_P	3.8 – 7.7 L/min	0.3 – 1.7 L/min	5.3(1.3) L/min	14.2%	2.4 L/min	0.62

Table 2: Day-to-day reproducibility analysis.

	Participant 1's mean(STD)	Participant 2's mean(STD)	Participant 3's mean(STD)	Mean Coefficient of Variation	Repeatability coefficient	r (ANOVA)
V_D	118.8(16.5) ml	172.7(19.6) ml	141.6(23.7) ml	14.0%	55.8 ml	0.64
FRC	1.89(0.19) L	2.57(0.45) L	2.95(0.21) L	11.5%	0.85 L	0.74
Q_P	3.1(0.7) L/min	4.8(0.8) L/min	5.1(0.7) L/min	18.4%	2.1 L/min	0.66

, in which s_ω was the within-subject standard deviation. s_ω was estimated from the one-way ANOVA analysis [22]. The repeatability r by ANOVA was estimated as:

$$r = \frac{s_A^2}{\left(s_\omega^2 + s_A^2\right)} \tag{6}$$

, in which s_A^2 was the between-subject variance and s_ω^2 was the within-subject variance. s_ω^2 was given from standard one-way ANOVA analysis, whereas s_A^2 was calculated as:

$$s_\omega^2 = \frac{\text{between-subject mean square} - \text{within-subject mean square}}{N_0} \tag{7}$$

, in which between-subject mean square and within-subject mean square were given by the one-way ANOVA analysis. The weighted average number of observation per group N_0 was estimated as:

$$N_0 = \frac{1}{\text{number of subjects} - 1} \times \left(\sum n_i - \sum n_i^2 / \sum n_i\right) \tag{8}$$

, in which n_i was the number of repeated tests of subject i.

2) Accuracy in Functional Residual Capacity Measurement

44 healthy subjects (16 female and 28 male) with no history of cardiopulmonary disease volunteered to participate in this study. 5 were active smokers. Each participants FRC was measured by the ISD and a body plethysmograph (MasterScreen Body, Cardinal Health, Lung Function Laboratory, Churchill Hospital, Oxford) in a randomized order. The paired measurements were then compared using a Bland-Altman plot.

3) Assessment of comfort

Out of all participants, 18 who were tested by body plethysmography, spirometry, and the ISD were also asked to rate how they felt when performing the test on the scale of 1 to 10; with 1 being unbearable, 5 being acceptable, and 10 being very comfortable. They were also asked to rank their preferences between body plethysmography, spirometry, and the ISD.

III. Results

A. Repeatability

Within-Session Repeatability. The repeated measurements of V_D, FRC, Q_P for 17 participants over 2 hours were plotted in Fig 4(a-c) and the results are shown in table 1. Statistical analysis using ANOVA generated r-values of 0.90, 0.89, and 0.62 for the three parameters respectively, indicating that 10%, 11%, and 38% of the variation in the data was due to differences within each individual.

Day-to-day reproducibility. The repeated measurements for 3 participants over 16 days were plotted in Fig 5(a-c) and the results are shown in table 2.

B. Accuracy in Functional Residual Capacity Measurement

The mean (std) age of the 44 subjects are 26.4 (12.8) years. Bland Altman analysis was performed on FRC measurements by the IST and the body plethysmograph (Fig. 6). The x-axis displays the difference $FRC_{\text{IST}} - FRC_{\text{bodyplethysmograph}}$ and the y-axis displays the average $\left(FRC_{\text{IST}} + FRC_{\text{bodyplethysmography}}\right)/2$ between the two techniques. The mean BIAS (SD) was estimated as -0.68 L (0.42 L). The 95% limits of agreement were -1.50 L to 0.14 L. 95% confidence interval of the estimations of the BIAS, Upper limit of Agreement, and Lower limit of Agreement were also displayed as dash lines on Fig. 6.

C. Assessment of Comfort

A total of 18 participants who experienced the ISD, body plethysmograph, and spirometry completed the comfort questionnaire. The results are shown in Fig. 7. 14

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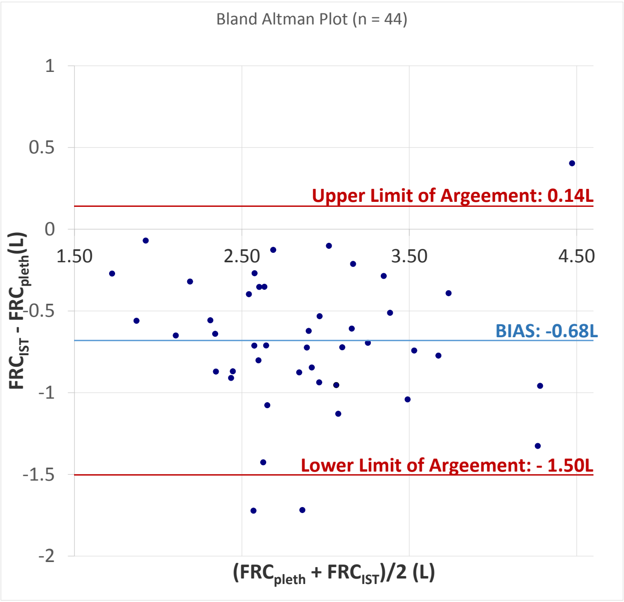

Fig. 6: Bland Altman plot comparing FRC measured by the inspired sinewave technique and by body plethysmography. Teal lines represents the bias and the limits of agreement. 95% confidence intervals of these estimates are shown in red dash lines. Legends: x-axis is (FRCISD + FRCpleth)/2; and y-axis is FRCISD – FRCpleth.

participants chose the ISD as their preferred test, and 15 rated the comfort of the ISD at 7 or above.

IV. Discussion

A. Repeatability

FRC measurements made using the ISD showed good within-session repeatability (CV=7.56%), which was comparable to that of other lung function tests in clinical use e.g. body plethysmography (CV=5%) [23] and multiple breath helium dilution (CV=5%) [24]. Measurements of Q_P and V_D, however, were less repeatable; in the case of Q_P, this may have been due to natural cardiac output variations over the two-hour testing period. The r-value of 0.62 suggested that this may have indeed been the case.

The day-to-day repeatability coefficients for V_D and Q_P were similar to that recorded within-sessions. The day-to-day repeatability coefficient for FRC was higher, 0.85 L compared to 0.48 L. The additional source of variation included day-to-day change in the environment's temperature and humidity. In fact, Fig 5(a) shows a correlation in V_D measurements between participants 1 and 2, which were taken on the same days especially on days 1 to 6. This suggested environmental factors likely influenced the measurements of our flow sensor. Future development should compensate for this factor to improve the accuracy and precision of the ISD.

Interestingly, subject 2 showed significantly and consistently lower FRC measurements between days 3 – 6 when he had a viral upper respiratory tract infection.

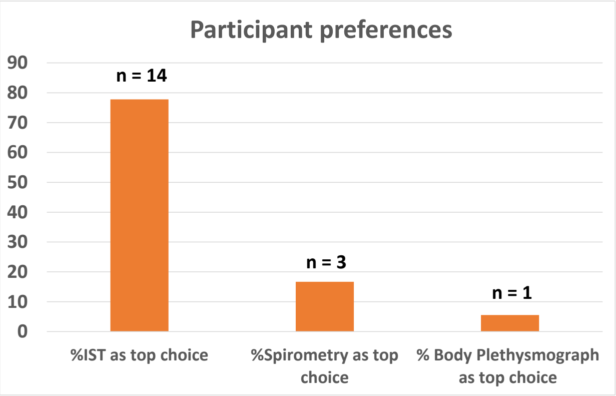

Fig. 7a

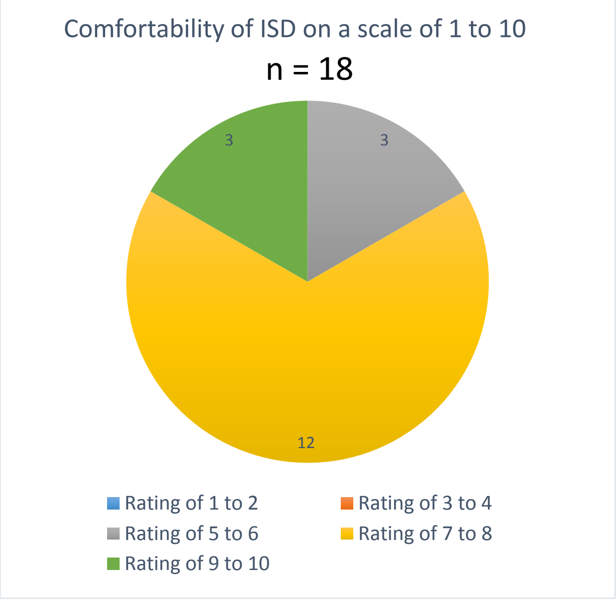

Fig. 7b

Fig. 7: Assessment of comfort between the ISD, body plethysmography and spirometry

Indeed, we have previously observed distinct differences between healthy volunteers and asymptotic asthma volunteers [20]. The study to determine how different lung inhomogeneity influences FRC measurements was beyond the scope of this paper but it would be a valuable future study.

B. Accuracy in Functional Residual Capacity Measurement

The BIAS (SD) of -0.68 (0.42) L showed that the ISD had similar precision to other techniques in the literature when compared with body plethysmography as the reference technique. Cliff et al. [25] reported that, helium dilution had a BIAS (SD) of -0.47 (0.48) L, mathematical modeling, had a BIAS (SD) of -0.53 (0.63) L, and nitrogen balance had a BIAS (SD) of -0.08 (0.48) L. In addition, O'Donnell et al. [26] reported a BIAS (SD) of -0.63 (0.22) L with helium dilution and, and a BIAS (SD) of -0.87 (0.21) L with CT scans. Lastly, Brewer and Orr [27] reported a

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BIAS (SD) of -0.054 (0.373) L with nitrogen washout, and -0.43 (0.91) L with CO2 rebreathing.

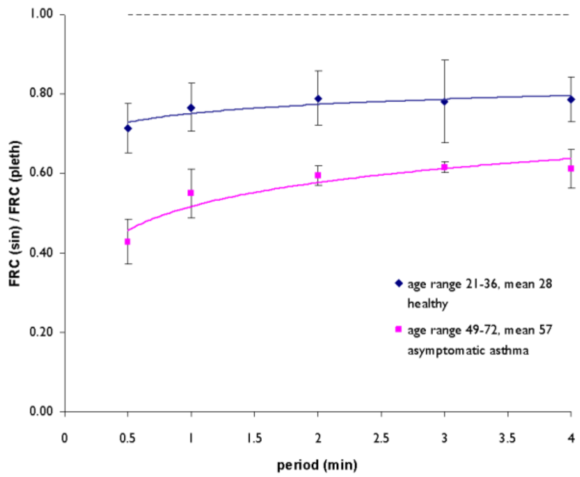

Fig. 8: When lung inhomogeneity presented, even in healthy volunteers, the FRC estimated from the ISD would depend on the inspired sinewave's frequency. The x-axis is the inspired sinewave period. The y-axis is the ratio between FRC estimated by the ISD and FRC estimated by body plethysmography. The mean ratios of two subject groups, healthy and asymptomatic asthma, are presented.

The negative bias of -0.68 L was also consistent with the widely accepted viewpoint that body plethysmography overestimates functional residual capacity compared to gas exchange techniques. This is principally because the latter techniques, by definition, only measure airspaces that participate in the gas exchange. The combined use of body plethysmography and gas dilution could give information about the volume of "trapped gas," which may be clinically useful [28], [29]. The authors therefore believe that agreement (or lack of) between the IST (or other gas exchange techniques) and body plethysmography should not be overemphasized as they essentially measured different volumes. For future research, as suggested by Ruppel [30], it would be more important to focus not only on the accuracy and repeatability, but also on integrating the results (the difference between the IST and body plethysmography in this case) into clinical decision making.

Another factor that could also contribute to the bias was lung inhomogeneity. When lung inhomogeneity presented, even in healthy volunteers, the FRC estimated from the ISD would depend on the inspired sinewave's frequency (Fig 8). The higher the frequency, the lower the estimated FRC. The dependency on the input frequency could potentially be used to assess lung inhomogeneity. In [20], we proposed the following indices to assess lung inhomogeneity:

$$I_1 = \frac{FRC(freq_2) - FRC(freq_1)}{FRC(freq_1)}$$

$$I_2 = \frac{FRC(predict)}{FRC(freq_1)}$$

$$I_3 = \frac{FRC(plethysmograph)}{FRC(freq_1)}$$

, in which $freq_1$, $freq_2$ are 2 different input frequencies, $FRC(plethysmograph)$ is the FRC measured by body plethysmography, and $FRC(predict)$ is the FRC predicted from the subject's height and weight.

There were some limitations to the presented study. Firstly, the presented study only included healthy volunteers, whereas other gas transfer techniques have been studied extensively in lung disease patients. Future studies should further investigate the ISD in lung disease patients. Secondly, for the reasons discussed above, there would always be a negative bias when comparing a gas transfer technique with body plethysmography. It would be advantageous for future studies to include an additional gas transfer technique as a comparator, such as helium dilution or multi-breath nitrogen washout.

C. *Assessment of Comfort*

The participants rated the use of the ISD as highly comfortable. All 18 participants rated it as acceptable to very comfortable. Impressively, 14 out of 18 volunteers preferred the ISD to the body plethysmograph and spirometer.

One limitation of this study was that our sample of participants was restricted to a relatively small group of healthy volunteers within a young age range 19 – 31. If the ISD is to be used as an alternative to standard lung function tests, it would be useful to assess it over a wider patient demographic, especially in young children and elderly patients, both of who are known to have difficulty obtaining reliable spirometry and body plethysmography data.

Two participants (out of 44) commented that they preferred to breathe through the mouth. In a previous design, subjects were asked to breathe through a mouthpiece with a nose clip. The majority reported this as uncomfortable due to dry mouths and tired jaws. It would be advantageous to incorporate a facial mask in a newer design of the ISD, in order to give users the option to breathe either through the mouth or nose. This new facial mask would need to take patient comfort, air tightness, and instrument dead space into consideration.

V. CONCLUSIONS

This paper presented the first comparison study of the inspired sinewave technique and device with body plethysmography for the measurements of functional residual capacity. Mean, standard deviation, coefficient of variation, repeatability coefficient, ANOVA and Bland-Altman plots were used to analyse repeatability and accuracy. The repeatability and accuracy of functional residual capacity was found to be as good as other techniques such as helium dilution and nitrogen washout when comparing with the body plethysmography in existing literature.

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The source of variation and disagreement between the ISD and the comparator techniques could be either technical, due to physiological difference or environmental factors such as temperature and/or humidity. Future work should include improving the accuracy of the device against changes in the environment's temperature and humidity and studying the effect of lung inhomogeneity on the device measurements.

Finally, the high level of comfort reported by participants and other advantages, including the non-requirement of patient effort and simultaneous measurements of FRC and blood flow, confirms that the ISD has the potential to be a useful alternative to other techniques if the aforementioned shortcomings are addressed. In particular, the ISD could be useful when assessing difficult patient groups such as the very young children, elderly, and ventilated patients. The results of this study justify further research and development of the inspired sinewave technique and device.

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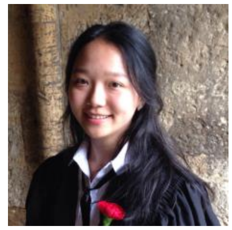
Phi Anh Phan received a Ph.D. degree in Artificial Intelligence and Nonlinear Control and a B.E. in Mechatronics from the University of Tasmania, Australia. His research interests include medical devices, robotics, and artificial intelligence. He has extensive R&D experience in respiratory medical devices, gained in Australia and the UK. He is a research fellow in the Nuffield Division of Anaesthetics, University of Oxford and an enterprise fellow of the Royal Academy of Engineering, UK.



Cathy Zhang received a BA in Cell and Systems Biology (First Class Honours) in 2014 from New College, the University of Oxford, Oxford, U.K., for which she was awarded the Gibbs Prize. She is currently a fourth-year medical student at King's College London, London, U.K. Her academic interests include respiratory and sleep medicine, intensive care medicine and medical education.

Federico Formenti received a D.Phil. degree in human physiology from the University of Oxford, Oxford, U.K., in 2011, and a Ph.D. degree in human biomechanics from Manchester Metropolitan University, Manchester, U.K., in 2006. He is currently a Senior Lecturer in the Faculty of Life Sciences and Medicine at King's College London, and a Honorary Senior Research Fellow in the Division of Anaesthetics, Nuffield Department of Clinical Neurosciences, University of Oxford. His research interests include human responses to hypoxia, exercise physiology, development of technology for physiological research, and critical care.

Clive E.W. Hahn is an Emeritus Professor of anaesthetic science with the Nuffeld Department of Anaesthetics, University of Oxford, Oxford, U.K., and was a Consultant in clinical measurement with Oxford University Hospitals NHS Trust, Oxford. He trained in Manchester, Sheffield, and Oxford, and originally took up NHS posts in the Oxford United Hospitals before becoming a University Lecturer of anaesthetics, and then gaining his professorial appointment and finally becoming the Head of the Oxford Anaesthetics Department. His current research interests include cardiopulmonary gas exchange in the sick and healthy lung, and gas and anaesthetic agent sensors. He is a fellow of the Royal Society of Medicine. He was a fellow of the Academy of Medical Sciences in 2000 and was awarded the Gold Medal of the Royal College of Anaesthetists in 2001.

Andrew D. Farmery studied Physiology and trained in Medicine and Anaesthetics in London, Cambridge and Oxford (UK) where he received a research fellowship in the Nuffield Division of Anaesthetics. He is the Fellow & Tutor in Medicine, and head the undergraduate programme at Wadham Colllege, University of Oxford, UK, which requires him to keep thinking beyond the respiratory system.